



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2016

Medical therapy of heart failure with reduced ejection fraction: current evidence and new developments

Naegele, Matthias ; Flammer, Andreas J ; Enseleit, Frank ; Ruschitzka, Frank

Abstract: Heart failure with reduced ejection fraction (HFrEF) is a common cardiovascular condition with a significant individual and societal burden. Although it was previously known as a palliative condition, medical drug therapies that were developed in the last four decades significantly reduced morbidity and mortality of the disease. The cornerstone of HFrEF therapy remains the blockade of the renin-angiotensin-aldosterone and the β -adrenergic systems. This review aims to give an overview and update on established disease-modifying therapies in HFrEF, discuss advances and setbacks in the treatment of selected comorbidities and provide an outlook on upcoming therapies including the new concept of dual angiotensin receptor and neprilysin inhibition.

DOI: <https://doi.org/10.4414/smw.2016.14295>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-134334>

Journal Article

Published Version



The following work is licensed under a Creative Commons: Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.

Originally published at:

Naegele, Matthias; Flammer, Andreas J; Enseleit, Frank; Ruschitzka, Frank (2016). Medical therapy of heart failure with reduced ejection fraction: current evidence and new developments. Swiss Medical Weekly, 146:w14295.

DOI: <https://doi.org/10.4414/smw.2016.14295>

Medical therapy of heart failure with reduced ejection fraction: current evidence and new developments

Matthias Naegele, Andreas J. Flammer, Frank Enseleit, Frank Ruschitzka

University Heart Centre, Cardiology, University Hospital Zurich, Switzerland

Summary

Heart failure with reduced ejection fraction (HFrEF) is a common cardiovascular condition with a significant individual and societal burden. Although it was previously known as a palliative condition, medical drug therapies that were developed in the last four decades significantly reduced morbidity and mortality of the disease. The cornerstone of HFrEF therapy remains the blockade of the renin-angiotensin-aldosterone and the β -adrenergic systems. This review aims to give an overview and update on established disease-modifying therapies in HFrEF, discuss advances and setbacks in the treatment of selected comorbidities and provide an outlook on upcoming therapies including the new concept of dual angiotensin receptor and neprilysin inhibition.

Key words: heart failure with reduced ejection fraction; HFrEF; medical therapy; comorbidities

Introduction

Heart failure is a clinical syndrome characterised by an inability of the heart to supply tissues with enough blood to meet their metabolic demands. It has various aetiologies and can be seen as the common final denominator of many cardiovascular conditions. In most cases it presents as a slowly progressing condition termed chronic or congestive heart failure. The clinical course is often superimposed by

acute episodes of worsening of signs and symptoms, also known as acute decompensated heart failure (ADHF).

The disease poses a major medical and economic challenge. In a recent European registry, nearly 20% of patients hospitalised for heart failure died and 50% were rehospitalised within the first year [1]. Long-term prognosis was found to be worse than several malignant cancers [2]. Based on US data, the prevalence of heart failure is expected to rise by nearly 50% from 2012 to 2030, largely as a result of the aging population. In this period, heart failure-related medical costs could rise from 20.9 to 53.1 billion US dollars [3], with a current average cost of 10.775 US dollars for a single heart failure hospitalisation [4].

Two types of heart failure are clinically distinguished based on assessment of systolic function: heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). The distinction is relevant as effective disease-modifying therapies are available only for HFrEF, while no clearly effective evidence-based treatments are available for HFpEF so far. This review aims to reflect on current disease-modifying drug treatments for chronic HFrEF and give an update on selected comorbidities and upcoming therapeutic concepts. For an overview on current therapeutic developments in HFpEF, ADHF, medical devices or cardiac biomarkers, interested readers are referred elsewhere [5–8].

Established disease-modifying therapies in HFrEF

Classical neurohormonal blockers

Neurohormonal blockers form the basis of disease-modifying therapy in chronic HFrEF (fig. 1). Current first-line neurohormonal blockers are angiotensin converting-enzyme (ACE) inhibitors to reduce renin-angiotensin-aldosterone system (RAAS) activation, and β -blockers to reduce adrenergic effects on the heart and thereby the heart rate. Combined neurohormonal blockade has revolutionised treatment of HFrEF since pivotal randomised controlled trials in the late 1980s and 1990s demonstrated its overwhelming benefit on hard endpoints. The current 2012 European Society of Cardiology (ESC) guidelines on heart failure recommend an ACE inhibitor and a β -blocker for all patients with symptomatic heart failure (New York Heart

Abbreviations

ACE	angiotensin converting-enzyme
ADHF	acute decompensated heart failure
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor (ARNI)
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LVEF	left ventricular ejection fraction
MRA	mineralocorticoid receptor antagonist
NYHA	New York Heart Association
RAAS	renin-angiotensin-aldosterone system
SGLT2	sodium-glucose co-transporter 2
SSRI	selective serotonin reuptake inhibitor

Association [NYHA] class II–IV) and a left ventricular ejection fraction (LVEF) $\leq 40\%$ to reduce heart failure hospitalisations and the risk of death [9]. An angiotensin receptor blocker (ARB) is recommended as an alternative for patients who do not tolerate an ACE inhibitor. Combination of an ARB with an ACE inhibitor is recommended only in patients who do not tolerate a mineralocorticoid receptor antagonist (MRA). Evidence-based agents of these drug classes should be chosen and titrated according to the dosing schemes of randomised controlled trials that demonstrated their benefit (“start low, go slow, aim high”) [9]. Slow uptitration is especially recommended for β -blockers, which, because of their negative inotropic effect, can transiently worsen heart failure.

Since the positive results of valsartan/sacubitril (LCZ696) in HFrEF (details below), guideline recommendations on RAAS blockers are expected to be revised. The new ESC guidelines on heart failure will be presented first in May 2016.

Mineralocorticoid receptor antagonists and ivabradine

Mineralocorticoid receptor antagonists (MRAs) represent the third class of disease-modifying agents in HFrEF since the striking results of the RALES and EPHESUS trials [10, 11]. An MRA is recommended in patients with an LVEF $\leq 35\%$ who remain symptomatic (NYHA class II–IV) on established ACE inhibitor (or ARB) and β -blocker therapy

[9]. The optimal LVEF threshold for initiating spironolactone may be higher, according to a recent *post-hoc* analysis of the overall neutral TOPCAT trial [12]. However, a designated trial in the intermediate LVEF range is necessary for clear recommendations.

The fourth disease-modifying guideline-recommended drug is ivabradine, a funny channel blocker that reduces heart rate in patients with sinus rhythm. Patients who still remain symptomatic, are in sinus rhythm and have a heart rate at or over 70 beats per minute despite maximum tolerated β -blocker dose should receive ivabradine to reduce heart failure hospitalisations and death from heart failure, according to the ESC guidelines [13].

Digoxin and hydralazine / isosorbide dinitrate

Besides these four drug classes and the use of device therapy (not part of this review), two other drugs are currently recommended for selected patients with HFrEF. Digoxin, which was popular before the advent of neurohormonal blockers, may be considered for patients with atrial fibrillation in addition to a β -blocker to control heart rate, in patients who do not tolerate a β -blocker or in patients who are still symptomatic on established ACE inhibitor (or ARB), β -blocker and MRA therapy. This recommendation is mainly based on the DIG trial, which was conducted before β -blockers were used commonly and which showed a reduction in heart failure hospitalisations with digoxin [14]. Prospective studies suggested that digoxin therapy is associated with increased mortality in patients with atrial fibrillation, but this result could not be corroborated in more recent analyses with more careful adjustment for confounding factors [15]. Regular monitoring of kidney function, keeping potassium levels in the normal and digoxin levels in the low-normal range, along with careful assessment of drug interactions (i.e., with amiodarone) may help reduce side effects of digoxin such as arrhythmias. The second drug recommended for selected patients is the combination of hydralazine with isosorbide dinitrate. It may be considered as an alternative to an ACE inhibitor or ARB if neither is tolerated or as an add-on therapy in still symptomatic patients, especially in patients of African-American origin.

Diuretics

Diuretics, although representing one of the oldest drug classes, still have insufficient data supporting a disease-modifying effect in chronic HFrEF. The few and small randomised trials available suggest a beneficial effect on mortality compared with placebo [16]. In contrast, in observational studies diuretic use is dose-dependently associated with increased mortality [17]. This association may be mediated by confounding factors (i.e., sicker heart failure patients are prescribed higher doses of diuretics). Given that the association was also observed in a recent propensity-matched observational study [18], a cautious use of diuretics in heart failure seems warranted. In regular clinical practice, diuretic use is often inevitable to successfully manage congestion. The ESC guidelines recommend diuretic use (preferentially loop diuretics) to relieve symptoms and signs congestion using the minimally necessary dose. Based on small clinical studies and pharmacokinetic con-

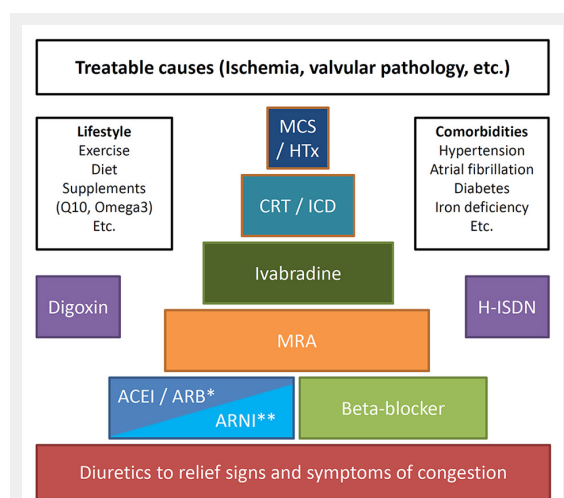


Figure 1

Overview on current therapies for heart failure with reduced ejection fraction (HFrEF). The pyramid depicts the step-wise approach of adding evidence-based treatments as recommended by the 2012 ESC guidelines [9]. The white boxes reflect additional factors that are important for the treatment of HFrEF independent of the standard treatments. Not all therapies are subjects of this review and for detailed recommendations review of the guidelines is recommended [5].

*An ARB is recommended when an ACEI is not tolerated

** The position of ARNIs in the treatment cascade will be defined in the next ESC heart failure guidelines and was thus not more clearly defined in this figure.

ACEI = angiotensin converting-enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; CRT = cardiac resynchronisation therapy; ICD = implantable cardioverter defibrillator; H-ISDN = hydralazine-isosorbide dinitrate; HTx = heart transplantation; MCS = mechanical circulatory support; MRA = mineralocorticoid antagonist; omega3 = omega-3 polyunsaturated fatty acids; Q10 = coenzyme Q10.

siderations, torasemide may be superior to the more commonly used furosemide, although evidence is still insufficient for a widespread recommendation [19].

New evidence on the use of neurohormonal blockers

Improving titration of neurohormonal blockers

The benefits of ACE inhibitors, ARBs and β -blockers stem from randomised controlled trials where these agents were titrated to target doses as tolerated. This strategy is supported by prospective evidence showing that titration to higher target doses is associated with better outcomes than staying on lower doses [20–22]. However, guideline-recommended usage of these drugs is still suboptimal in real-world clinical practice. In a large Danish registry, the proportion of heart failure patients on ACE inhibitors, ARBs, β -blockers and spironolactone was low, and most patients did not receive the recommended target doses [23]. This observation was recently reinforced in the international observational QUALIFY study that was presented at the 2015 European Heart Failure Congress [24]. In this study, only 28% of patients on ACE inhibitors, 7% of patients on ARBs, 15% on β -blockers and 71% of patients on MRAs received the recommended target doses. This discrepancy may be explained by differences between patients included in randomised trials and patients in real-world clinical practice where a higher morbidity burden may reduce tolerance of target doses. Doctors' fear of certain side effects (i.e., worsening renal function, changing potassium levels) may also play a role in not uptitrating therapy. Interestingly, programmes designed to improve physician education and implementation of guidelines showed that a higher rate of target doses can be safely achieved in regular outpatient settings [25, 26]. Lack of communication between hospital and outpatient physicians may be an issue in this regard. For instance, heart failure patients eligible for disease-modifying therapy who were not prescribed a β -blocker at hospital discharge were significantly less likely to receive one at follow-up [27]. Given that patients who were prescribed a β -blocker at discharge have a significantly lower risk of death and rehospitalisation [27], better physician training and communication between cardiologists and general physicians may be helpful in improving guideline adherence and patient outcomes.

Prescription of β -blockers may also be improved by focusing on the reduction in heart rate. Some studies indicated that the magnitude of heart rate reduction by β -blockers rather than the achieved drug dose is important [28, 29]. The importance of heart rate is also supported by data on ivabradine indicating that reaching a heart rate of under 60 beats per minute is associated with the lowest event rates [30]. However, the optimal target heart rate in HFrEF patients is still unknown as the large trials focused on target drug doses rather than achieved heart rate reduction. Hence, trying to reach the maximum tolerated target β -blocker doses still appears to be the most evidence-based approach, which is also supported by a recent analysis [31].

Safety and benefit of RAAS blockers in advanced chronic kidney disease

A common clinical question is how to use ACE inhibitors, ARBs and MRAs in patients with moderate to severe chronic kidney disease. Renal insufficiency is a major comorbidity in heart failure and the extent of estimated glomerular filtration rate (eGFR) impairment correlates more strongly with mortality than left ventricular ejection fraction [32]. The question was recently dealt with in a review of randomised controlled trials [33]. The authors concluded that there is strong supporting evidence for ACE inhibitors and MRAs and moderate evidence for ARBs in heart failure patients with stage 3 kidney disease (eGFR 30–59 ml/min/1.73 m²). For patients with stage 4–5 kidney disease (eGFR <30 ml/min/1.73 m²), evidence from randomised trials for ARBs and MRAs is not available. For ACE inhibitors, weak evidence supporting their cautious use in these stages is available. A recently published propensity-matched cohort study from Sweden showed that ACE inhibitor or ARB use was associated with reduced mortality in heart failure patients with an eGFR <30 ml/min/1.73 m² [34]. The relative reduction was similar to that observed in patients with less severe renal insufficiency and echoes the results of a prior observational study [35]. Given the significantly higher mortality rate of patients with severe renal insufficiency, ACE inhibitor use may be associated with an even higher absolute mortality reduction in this population. This represents a strong rationale for randomised trials in patients with advanced chronic kidney disease. Until such studies are available, a cautious use of these agents in chronic kidney disease, with regular monitoring of serum potassium and creatinine, is warranted. It is worth noting that a certain degree of worsening renal function and/or increase in potassium levels is to be expected after initiating ACE inhibitors, ARBs or MRAs. It is part of the mechanism of action of these drugs and does not indicate an adverse outcome [33, 36]. In line with this, a recent observational study showed that use of high-dose diuretics but not spironolactone, β -blockers or RAAS blockers was associated with worse outcomes in worsening renal function [36]. Regarding ACE inhibitors and ARBs, an increase of creatinine up to 50% above baseline or an eGFR of up to 25 ml/min/1.73 m², whichever is smaller, and a potassium level of ≤ 5.5 mmol/l is considered acceptable, according to expert opinion [9]. Regarding MRAs, potassium levels of ≤ 5.5 mmol/l and an eGFR of up to 30 ml/min/1.73 m² are acceptable [9]. Further alterations should result in dose reductions or discontinuation as necessary. Another factor that should be appreciated is that renal dysfunction in heart failure is often caused by venous congestion and not only by low arterial perfusion [37]. In this situation, decongestive therapy and prevention of decompensations with neurohormonal blockers is a key element to preserve renal function.

Beta-blockers in HFrEF patients with atrial fibrillation

The benefit of β -blockade in HFrEF patients in sinus rhythm is firmly established. Recently, new evidence has emerged for the use of β -blockers in HFrEF patients with atrial fibrillation. Prior randomised trials included only a small fraction of HFrEF patients with atrial fibrillation,

resulting in insufficient power to assess the effect of β -blockers in this common subpopulation. A recent individual patient data meta-analysis showed that β -blockers reduce mortality only in HFrEF patients with sinus rhythm but not in patients with atrial fibrillation [38]. The results are surprising, as the reduction in heart rate by β -blockers was found to be similar in both groups. As an explanation, the optimum heart rate in patients with atrial fibrillation may be higher than in patients in sinus rhythm, according to a trial comparing strict with lenient rate control [39]. Alternative drugs such as amiodarone are problematic because of their long term toxicity. Digoxin may be a viable alternative, but, similarly, evidence is insufficient for its first-line use in atrial fibrillation. In the absence of alternatives and no evidence of harm, guidelines are currently unlikely to change and β -blockers will remain first-line therapy in HFrEF patients with atrial fibrillation. A larger randomised trial focused on HFrEF patients with atrial fibrillation that aims to identify the optimum heart rate may help to obtain more definitive answers.

New evidence on comorbidities in heart failure

Comorbidities such as diabetes, hypertension, dyslipidaemia or depression are a common feature in heart failure and their coexistence is often associated with a worse prognosis [40, 41]. Many of the associations can be explained by the systemic nature of heart failure and the complex interplay of risk factors and their effect on different organs including the heart. Successful therapy of comorbidities holds the potential to improve prognosis further in heart failure patients. While significant advances were made with certain comorbidities such as with hypertension (i.e., better blood pressure control using evidence-based drug combinations) or atrial fibrillation (i.e., novel oral anticoagulants), other fields experienced setbacks in recent years. Some recent developments on selected comorbidities are reviewed below.

Diabetes

Diabetes is highly prevalent in heart failure and associated with a worse prognosis [42]. Most available antidiabetic drugs have been approved on the basis of surrogate markers such as lowering of blood glucose and glycated haemoglobin. Evidence from postapproval studies indicates that this strategy may not have been optimal [43]. Glitazones, which were once popular oral antidiabetic agents, have been shown to increase water retention and increase the risk for heart failure [44]. One of member of this group, rosiglitazone, may even adversely affect other cardiovascular outcomes such as myocardial infarction [45, 46]. Sulfonylurea drugs may also be problematic, according to observational studies indicating an increased risk of heart failure [47, 48]. The newer class of dipeptidyl peptidase-4 inhibitors has also recently been subject of closer scrutiny when one of its members, saxagliptin, was shown to increase heart failure hospitalisations without demonstrating a benefit on other cardiovascular events [49]. This increase was not seen with sitagliptin, but similarly, no reduction in cardiovascular events was observed [50]. Even insulin may

be problematic in heart failure, partly because of its ability to increase sodium and water retention. In observational studies, insulin therapy is consistently associated with worse outcomes in heart failure [51–54]. This observation may, however, be biased by prescribing patterns, as insulin is often given to patients with more advanced diabetes [55]. While these data paint a rather dark picture of current antidiabetic drugs, it is reassuring that the current first-line drug metformin appears to be safe in heart failure and may even be superior to other established agents [52, 56, 57]. Metformin dose should be adjusted according to renal function and treatment is not recommended in patients with an eGFR <30 ml/min/1.73 m² owing to its potential to cause lactic acidosis.

Beyond established drugs for diabetes, the field of antihyperglycaemic therapy is expected to change significantly since publication of a recent randomised trial on empagliflozin [58]. Empagliflozin belongs to the new drug class of sodium-glucose co-transporter 2 (SGLT2) inhibitors, which increase renal glycosuria. In the EMPA-REG OUTCOME trial, it significantly reduced both all-cause and cardiovascular mortality, making it one of the first antihyperglycaemic drugs with a well-documented effect on hard endpoints. Hospitalisations for heart failure were also significantly reduced by empagliflozin, possibly owing to its osmotic diuretic effect. This effect appeared to be similar in magnitude in patients with pre-existing heart failure in a *post-hoc* analysis [59]. Further trials focused on heart failure patients need to show the safety and efficacy of SGLT2-inhibitors especially in patients with impaired kidney function and concomitant diuretic therapy. Until these are available, cautious use in heart failure patients may be worthwhile in light of its osmotic diuretic effect and the chance of delaying initiation of insulin therapy. Urinary tract infections, genital infections, ketoacidosis and volume depletion are potential side effects.

Depression

Depression is a common comorbidity associated with a significant morbidity burden. The current ESC heart failure guidelines recommend psychosocial intervention and pharmacological treatment, preferably with selective serotonin reuptake inhibitors (SSRIs) [9]. Previously, only one larger randomised controlled trial with an SSRI in heart failure patients with depression, SADHART-CHF, was available [60]. In this trial, sertraline was ineffective in reducing depression or improving cardiovascular status compared with placebo. Recently, results of the MOOD-HF trial were presented at the 2015 ESC heart failure congress [61]. This trial studied the long-term effects of escitalopram on mortality, hospitalisations and depression symptoms in HFrEF patients with major depression compared with placebo and, in addition, to optimal medical therapy. Similar to SADHART-CHF, escitalopram neither reduced mortality and hospitalisations, nor reduced depression symptoms compared with placebo. In a *post-hoc* subgroup analysis, escitalopram appeared to worsen mortality and hospitalisation rates in patients with more advanced heart failure, whereas it seemed to benefit patients with milder HFrEF. These results argue for a more cautious use of antidepressants in HFrEF patients. SSRIs can cause significant drug

interactions as a result of their hepatic metabolism, and some agents prolong the QT interval and may be arrhythmogenic. In both trials, there was a pronounced reduction in depression symptoms in both the placebo and the SSRI group over time, suggesting that depression in heart failure can also resolve on its own and may be already alleviated by providing regular patient contacts and optimising heart failure therapy.

Dyslipidaemia

A relevant controversy also exists on dyslipidaemia and the question of whether to treat heart failure patients with statins. In two large randomised controlled trials with rosuvastatin, CORONA and GISSI-HF, there was no improvement in mortality or reduction in coronary events in HFrEF patients [62, 63]. The results are surprising given that in CORONA only patients with ischaemic heart failure were included and in GISSI-HF a majority of patients had heart failure of ischaemic origin without signs of an interaction between ischaemic and nonischaemic heart failure. Despite this neutral effect on mortality, a recent reanalysis of the CORONA trial showed that rosuvastatin reduced repeat heart failure hospitalisations [64]. Likewise, in patients without heart failure, statins may be able to prevent heart failure hospitalisations but without affecting heart failure mortality [65]. Several theories about the inefficacy of statins in heart failure are discussed. One is that in ischaemic heart failure the ischaemic insult has already occurred and the attenuation in coronary artery disease progression does not significantly affect the overall clinical course. Cholesterol may also serve a protective role in heart failure, for instance by binding and neutralising endotoxin [66] or by serving as the basis for the synthesis of protective steroid hormones and cofactors such as coenzyme Q10 [67]. Another theory is that hydrophilic statins like rosuvastatin have a lower penetration into heart tissue and lipophilic statins such as atorvastatin may be more efficacious [68]. Given these uncertainties, the current guidelines do not recommend initiating statins in most patients with chronic heart failure [9].

Gout

Another frequent comorbidity in heart failure is gout. Gout is often precipitated by diuretic therapy and therapy of gout attacks is complicated by the cardiac adverse effects of nonsteroidal anti-inflammatory drugs and corticosteroids. Uric acid levels are frequently elevated in heart failure patients, predict outcome [69] and correlate with gout risk [70]. It was hoped that the answer was to reduce uric acid with xanthine oxidase inhibitors. The recently published EXACT-HF study compared the effects of allopurinol in HFrEF patients with elevated uric acid levels with those of placebo [71]. Unfortunately, allopurinol had no effect on clinical outcomes, echocardiographic measures, heart failure symptoms and physical capability. The results echo those of the earlier OPT-CHF study, which failed to show effectiveness of oxypurinol in HFrEF [72]. A recent Mendelian randomisation study also failed to show an association of genetically-associated uric acid levels with heart failure and other cardiovascular diseases [73]. The negative results may be explained by possible protective

effects of uric acid, which is quantitatively the most important antioxidant in human blood and may represent a marker of response to increased oxidative stress [74]. Although general reduction of uric acid in HFrEF regardless of symptoms may not be helpful, selective treatment of HFrEF patients with gout may still be beneficial, as indicated by a prospective study [75]. We therefore recommend restricting xanthine oxidase inhibitor treatment to patients with a clinical diagnosis of gout and adapting its dose to renal function. Acute flares should be treated with colchicine rather than nonsteroidal anti-inflammatory drugs [9]. In our centre, we have good experience with short courses of oral prednisone for the treatment of gout flares, although we acknowledge its potential to cause acute decompensations.

Iron deficiency

Interest in iron deficiency was renewed in recent years with the advent of intravenous iron therapy. Iron deficiency is common in HFrEF and its presence correlates with a worse prognosis [76]. Two randomised controlled trials showed that intravenous iron therapy in HFrEF patients with iron deficiency improves physical capability, heart failure symptoms, quality of life and fatigue [77, 78]. A recent meta-analysis that included both trials showed a significant reduction in heart failure hospitalisations [79]. The effect on hard endpoints such as cardiovascular or all-cause mortality is still unclear and needs to be tested in a larger confirmatory trial [80]. To assess HFrEF patients for intravenous iron therapy it is recommended to use the same diagnostic criteria that were used in both trials (ferritin <100 ng/ml or ferritin 100–300 ng/ml if transferrin saturation is <20%) and employ similar dosing schemes.

New therapeutic strategies in HFrEF

Several new therapeutic strategies for chronic HFrEF are in advanced clinical development. Owing to space constraints this review will focus on the newly approved angiotensin receptor neprilysin inhibitor (ARNI) valsartan/sacubitril, third-generation MRAs, new ways to manage hyperkalaemia as well as approaches to improve cardiac metabolism. Other notable examples in development are the soluble guanylate cyclase stimulator vericiguat that modulates the NO-cGMP system (SOCRATES study programme) [81], the renin inhibitor aliskiren, which reduces RAAS activation (ATMOSPHERE study) [82] or low-dose anticoagulation with rivaroxaban in HFrEF patients without an established indication for anticoagulation (COMMANDER-HF study) [83].

Dual angiotensin receptor and neprilysin blockade

Valsartan/sacubitril is a dual angiotensin receptor neprilysin inhibitor that consists of a 1:1 mixture of the ARB valsartan and the neprilysin inhibitor sacubitril. Neprilysin inhibitors decrease degradation of various vasoactive peptides, including the potentially cardioprotective natriuretic peptides. Recently, results were published from the large PARADIGM-HF trial, which compared valsartan/sacubitril with enalapril in HFrEF patients [84]. The fixed combination significantly reduced all-cause and cardiovascular

mortality as well as hospitalisations for heart failure compared with enalapril. Thereby, PARADIGM-HF was the first heart failure trial to show that replacement of a class 1A guideline-recommended drug, an ACE-inhibitor, with a new drug resulted in an incremental improvement in outcome. The product is already approved in Switzerland and upcoming heart failure guidelines are expected to be adapted to the new evidence.

To improve clinical implementation, several characteristics of the drug should be taken into consideration. First, PARADIGM-HF employed a run-in period resulting in only patients tolerating both ACE-inhibitor and valsartan/sacubitril treatment to enter the randomised treatment period. Based on the drop-out rates in the run-in period, not all heart failure patients are expected to tolerate the drug in real world clinical practice. A common side effect is symptomatic hypotension, which occurs more frequently with valsartan/sacubitril than with enalapril. Interestingly, despite this observation, hyperkalaemia and renal impairment were less frequent with valsartan/sacubitril [84]. Another concern is the risk of angioedema, which was numerically but not significantly increased in the trial. Because of this, concomitant therapy with an ACE inhibitor or aliskiren is contraindicated and combination with another ARB is not advised. Because of the degradation of amyloid peptides by neprilysin, an increase in neurodegenerative disease is a theoretical concern [85]. Although no signals of an increase in dementia or cognitive impairment were seen in the PARADIGM-HF trial [84], the effect of valsartan/sacubitril on cognitive function will be assessed in more detail in currently running trials.

Third-generation MRAs and management of hyperkalaemia

Mineralocorticoid receptor blockade is another area with new developments. Even though MRAs are highly effective in HFrEF, one of the main issues limiting their use is hyperkalaemia [86]. The currently available MRAs spironolactone and eplerenone have a relatively high tissue concentration in the kidney, where mineralocorticoid receptor antagonism increases renal potassium retention. This led to the development of finerenone, a nonsteroidal MRA, with a more balanced tissue distribution between the heart and kidney. In a phase II study, it led to a smaller increase in potassium than spironolactone with a comparable reduction in natriuretic peptide levels [87]. It showed promising results in a recently presented phase IIb study [88] and development is expected to enter phase III.

New strategies to manage potassium levels are also emerging. Two new drugs, sodium zirconium cyclosilicate and patiromer, which remove potassium by binding it in the gut, were recently shown to reduce hyperkalaemia in susceptible patients [89, 90]. Future trials will need to show their safety and efficacy in heart failure. If positive, they might allow more consistent MRA use in patients with advanced chronic kidney disease.

Cardiac metabolism and mitochondrial function

An exciting field in which interest was recently renewed is cardiac metabolism and mitochondrial function in heart failure [91]. Research on cardiac metabolism was very active

in the first half of the 20th century but interest waned with the onset of therapies that primarily focused on haemodynamic modulation. Evidence is accumulating that mitochondrial dysfunction plays a central role in heart failure [92]. One particular feature of heart failure appears to be the loss of cardiolipin [93]. Cardiolipin is a mitochondrial membrane lipid that stabilises the electron transport chain and thereby maintains energy production. SS-31 (Bendavia) is a novel tetrapeptide that binds to cardiolipin and appears to restore electron transport chain functionality [94]. Phase II studies are ongoing in heart failure and other conditions.

Coenzyme Q10 is a vitamin-like quinone that serves as an electron carrier between respiratory chain complexes. It has been under investigation for heart failure for quite some time, but prior studies were too small and heterogeneous to allow firm conclusions [95]. Last year, results from the largest and most rigorous study, the Q-SYMBIO trial, were published [96]. The trial met its primary endpoint and showed that coenzyme Q10 reduces all-cause and cardiovascular mortality as well as heart failure hospitalisations and symptoms. Hopefully, the results of this trial are sufficient to renew interest in this nonpatentable substance. Replication of these findings is important, as is improved quality control and standardisation of dosing of coenzyme Q10 supplements before widespread recommendations can be made.

Conclusion

With the onset of neurohormonal blockade, tremendous progress has been made in the medical treatment of HFrEF in the last three decades. New evidence on how to optimise treatment using established disease-modifying treatments is available and their implementation may improve prognosis of our patients. Treatment for several comorbidities such as diabetes and iron deficiency has improved while neutral results in others urge us to think over our pathophysiological concepts. Despite the progress, HFrEF still remains a deadly condition in 2016 and new effective therapies are urgently needed. New therapeutic principles such as dual angiotensin receptor neprilysin blockade raise hope that the burden of heart failure can further be reduced in the coming years.

Disclosure statement: MN: No conflict of interest. AF: Bayer (advisory board, research support), Novartis (advisory board). FE: No conflict of interest. FR: Biotronik (advisory board), Cardiorientis (research grant, advisory board), Servier (speakers bureau).

Correspondence: Matthias Naegele, MD, University Hospital Zurich, University Heart Center, Rämistrasse 100, CH-8091 Zurich, [matthias.naegele\[at\]usz.ch](mailto:matthias.naegele[at]usz.ch)

References

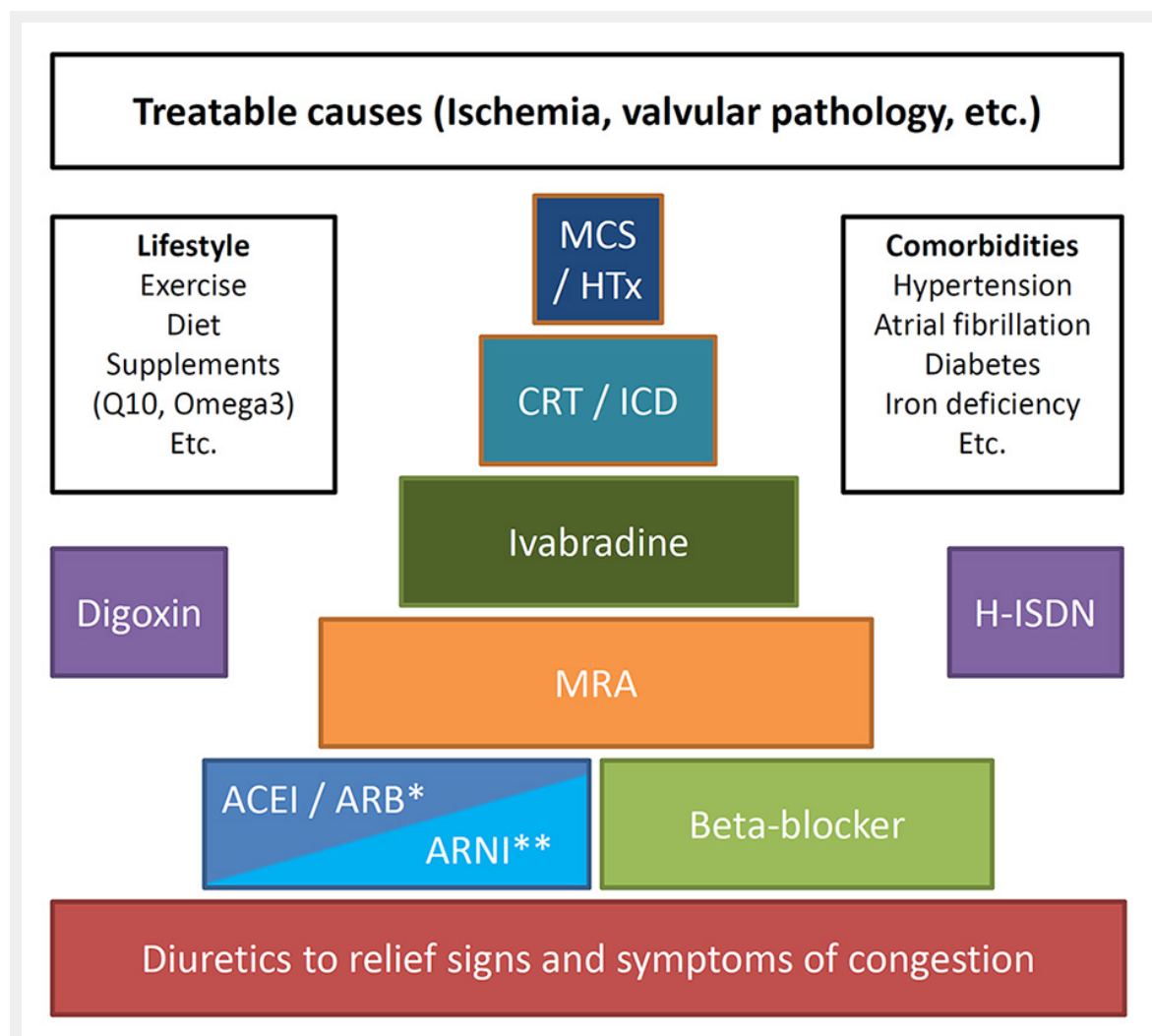
- 1 Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Crespo Leiro M, Drozd J, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail.* 2013;15(7):808–17.

- 2 Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More "malignant" than cancer? Five-year survival following a first admission for heart failure. *Eur J Heart Fail.* 2001;3(3):315–22.
- 3 Heidenreich PA, Albert NM, Allen LA, Blumke DA, Butler J, Fonarow GC, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail.* 2013;6(3):606–19.
- 4 Ziaiean B, Sharma PP, Yu T-C, Johnson KW, Fonarow GC. Factors associated with variations in hospital expenditures for acute heart failure in the United States. *Am Heart J.* 2015;169(2):282–9.e15.
- 5 Senni M, Paulus WJ, Gavazzi A, Fraser AG, Diez J, Solomon SD, et al. New strategies for heart failure with preserved ejection fraction: the importance of targeted therapies for heart failure phenotypes. *Eur Heart J.* 2014;35(40):2797–815.
- 6 Hsiao R, Greenberg B. Contemporary Treatment of Acute Heart Failure. *Prog Cardiovasc Dis.* 2016. Epub Jan 4.
- 7 Marangou J, Paul V. Current attitudes on cardiac devices in heart failure: a review. *Clin Ther.* 2015;37(10):2206–14.
- 8 Pruett AE, Lee AK, Patterson JH, Schwartz TA, Glotzer JM, Adams KF. Evolution of biomarker guided therapy for heart failure: current concepts and trial evidence. *Curr Cardiol Rev.* 2015;11(1):80–9.
- 9 McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2012;33(14):1787–847.
- 10 Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med.* 1999;341(10):709–17.
- 11 Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 2003;348(14):1309–21.
- 12 Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J.* 2015. Epub Sep 15.
- 13 Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet.* 2010;376(9744):875–85.
- 14 Digitalis Investigation G. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med.* 1997;336(8):525–33.
- 15 Ziff OJ, Lane DA, Samra M, Griffith M, Kirchhof P, Lip GY, et al. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. *BMJ.* 2015;351:h4451.
- 16 Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. *Cochrane Database Syst Rev.* 2012;2:CD003838.
- 17 Felker GM, O'Connor CM, Braunwald E, Heart Failure Clinical Research Network I. Loop diuretics in acute decompensated heart failure: necessary? Evil? A necessary evil? *Circ Heart Fail.* 2009;2(1):56–62.
- 18 Damman K, Kjekshus J, Wikstrand J, Cleland JGF, Komajda M, Wedel H, et al. Loop diuretics, renal function and clinical outcome in patients with heart failure and reduced ejection fraction. *Eur J Heart Fail.* 2015. Epub Dec 23.
- 19 DiNicolantonio JJ. Should torsemide be the loop diuretic of choice in systolic heart failure? *Future Cardiol.* 2012;8(5):707–28.
- 20 Fiuzat M, Wojdyla D, Kitzman D, Fleg J, Keteyian SJ, Kraus WE, et al. Relationship of beta-blocker dose with outcomes in ambulatory heart failure patients with systolic dysfunction: results from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial. *J Am Coll Cardiol.* 2012;60(3):208–15.
- 21 Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet.* 2009;374(9704):1840–8.
- 22 Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation.* 1999;100(23):2312–8.
- 23 Gislason GH, Rasmussen JN, Abildstrom SZ, Schramm TK, Hansen ML, Buch P, et al. Persistent use of evidence-based pharmacotherapy in heart failure is associated with improved outcomes. *Circulation.* 2007;116(7):737–44.
- 24 Komajda M. Physician's adherence to evidence-based pharmacotherapy in systolic heart failure: data from international QUALIFY survey. ESC Heart Failure 2015 Congress. Presentation No. 540.
- 25 Peters-Klimm F, Muller-Tasch T, Remppis A, Szecsenyi J, Schellberg D. Improved guideline adherence to pharmacotherapy of chronic systolic heart failure in general practice – results from a cluster-randomised controlled trial of implementation of a clinical practice guideline. *J Eval Clin Pract.* 2008;14(5):823–9.
- 26 Jain A, Mills P, Nunn LM, Butler J, Luddington L, Ross V, et al. Success of a multidisciplinary heart failure clinic for initiation and up-titration of key therapeutic agents. *Eur J Heart Fail.* 2005;7(3):405–10.
- 27 Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Prospective evaluation of beta-blocker use at the time of hospital discharge as a heart failure performance measure: results from OPTIMIZE-HF. *J Card Fail.* 2007;13(9):722–31.
- 28 Gelbrich G, Edelmann F, Inkrot S, Lainscak M, Apostolovic S, Neskovic AN, et al. Is target dose the treatment target? Uptitrating beta-blockers for heart failure in the elderly. *Int J Cardiol.* 2012;155(1):160–6.
- 29 McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med.* 2009;150(11):784–94.
- 30 Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet.* 2010;376(9744):886–94.
- 31 Fiuzat M, Wojdyla D, Pina I, Adams K, Whellan D, O'Connor CM. Heart Rate or Beta-Blocker Dose? Association With Outcomes in Ambulatory Heart Failure Patients With Systolic Dysfunction: Results From the HF-ACTION Trial. *JACC Heart Fail.* 2016;4(2):109–15.
- 32 Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation.* 2000;102(2):203–10.
- 33 Damman K, Tang WH, Felker GM, Lassus J, Zannad F, Krum H, et al. Current evidence on treatment of patients with chronic systolic heart failure and renal insufficiency: practical considerations from published data. *J Am Coll Cardiol.* 2014;63(9):853–71.
- 34 Edner M, Benson L, Dahlström U, Lund LH. Association between renin-angiotensin system antagonist use and mortality in heart failure with severe renal insufficiency: a prospective propensity score-matched cohort study. *Eur Heart J.* 2015;36(34):2318–26.
- 35 Ahmed A, Kiefe CI, Allman RM, Sims RV, DeLong JF. Survival benefits of angiotensin-converting enzyme inhibitors in older heart failure patients with perceived contraindications. *J Am Geriatr Soc.* 2002;50(10):1659–66.
- 36 Brunner-La Rocca H-P, Knackstedt C, Eurlings L, Rolny V, Krause F, Pfisterer ME, et al. Impact of worsening renal function related to medication in heart failure. *Eur J Heart Fail.* 2015;17(2):159–68.
- 37 Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol.* 2009;53(7):589–96.
- 38 Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, et al. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet.* 2014;384(9961):2235–43.
- 39 Van Gelder IC, Groeneweld HF, Crijns HJGM, Tuininga YS, Tijssen JGP, Alings AM, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med.* 2010;362(15):1363–73.
- 40 Braunstein JB, Anderson GF, Gerstenblith G, Weller W, Niefeld M, Herbert R, et al. Noncardiac comorbidity increases preventable hos-

- pitalizations and mortality among medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol.* 2003;42(7):1226–33.
- 41 van Deursen VM, Urso R, Laroche C, Damman K, Dahlstrom U, Tavazzi L, et al. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. *Eur J Heart Fail.* 2014;16(1):103–11.
 - 42 Johansson I, Edner M, Dahlström U, Näsman P, Rydén L, Norhammar A. Is the prognosis in patients with diabetes and heart failure a matter of unsatisfactory management? An observational study from the Swedish Heart Failure Registry. *Eur J Heart Fail.* 2014;16(4):409–18.
 - 43 Holman RR, Sourij H, Califf RM. Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes. *Lancet.* 2014;383(9933):2008–17.
 - 44 Hernandez AV, Usmani A, Rajamanickam A, Moheet A. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. *Am J Cardiovasc Drugs.* 2011;11(2):115–28.
 - 45 Loke YK, Kwok CS, Singh S. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. *BMJ.* 2011;342:d1309.
 - 46 Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med.* 2010;170(14):1191–201.
 - 47 McAlister FA, Eurich DT, Majumdar SR, Johnson JA. The risk of heart failure in patients with type 2 diabetes treated with oral agent monotherapy. *Eur J Heart Fail.* 2008;10(7):703–8.
 - 48 Varas-Lorenzo C, Margulis A, Pladevall M, Riera-Guardia N, Calingaert B, Hazell L, et al. The risk of heart failure associated with the use of noninsulin blood glucose-lowering drugs: systematic review and meta-analysis of published observational studies. *BMC Cardiovascular Disorders.* 2014;14(1):129.
 - 49 Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. *N Engl J Med.* 2013;369(14):1317–26.
 - 50 Akiyama E, Sugiyama S, Matsuzawa Y, Konishi M, Suzuki H, Nozaki T, et al. Incremental prognostic significance of peripheral endothelial dysfunction in patients with heart failure with normal left ventricular ejection fraction. *J Am Coll Cardiol.* 2012;60(18):1778–86.
 - 51 Murcia AM, Hennekens CH, Lamas GA, Jiménez-Navarro M, Rouleau JL, Flaker GC, et al. Impact of diabetes on mortality in patients with myocardial infarction and left ventricular dysfunction. *Arch Intern Med.* 2004;164(20):2273–9.
 - 52 Nichols GA, Koro CE, Gullion CM, Ephross SA, Brown JB. The incidence of congestive heart failure associated with antidiabetic therapies. *Diabetes Metab Res Rev.* 2005;21(1):51–7.
 - 53 Smooke S, Horwich TB, Fonarow GC. Insulin-treated diabetes is associated with a marked increase in mortality in patients with advanced heart failure. *Am Heart J.* 2005;149(1):168–74.
 - 54 Mangiacavalli M, Gasparini M, Genovese S, Pini D, Klersy C, Bragato R, et al. Insulin-treated type 2 diabetes is associated with a decreased survival in heart failure patients after cardiac resynchronization therapy. *Pacing Clin Electrophysiol.* 2008;31(11):1425–32.
 - 55 Gilbert RE, Krum H. Heart failure in diabetes: effects of anti-hyperglycaemic drug therapy. *Lancet.* 2015;385(9982):2107–17.
 - 56 Eurich DT, Weir DL, Majumdar SR, Tsuyuki RT, Johnson JA, Tjosvold L, et al. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. *Circ Heart Fail.* 2013;6(3):395–402.
 - 57 MacDonald MR, Eurich DT, Majumdar SR, Lewsey JD, Bhagra S, Jhund PS, et al. Treatment of type 2 diabetes and outcomes in patients with heart failure: a nested case-control study from the U.K. General Practice Research Database. *Diabetes Care.* 2010;33(6):1213–8.
 - 58 Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med.* 2015;373(22):2117–28.
 - 59 Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. *Eur Heart J.* 2016. Epub Jan 26.
 - 60 O'Connor CM, Jiang W, Kuchibhatla M, Silva SG, Cuffe MS, Callwood DD, et al. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. *J Am Coll Cardiol.* 2010;56(9):692–9.
 - 61 Angermann C. Selective serotonin re-uptake inhibition in heart failure with co-morbid depression – differential effects on mortality, morbidity and psychometric outcome in MOOD-HF subgroups. ESC Heart Failure 2015 Congress. Presentation No. 542.
 - 62 Kjekshus J, Apetrei E, Barrios V, Bohm M, Cleland JG, Cornel JH, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med.* 2007;357(22):2248–61.
 - 63 Gissi HFI, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2008;372(9645):1231–9.
 - 64 Rogers JK, Jhund PS, Perez AC, Bohm M, Cleland JG, Gullestad L, et al. Effect of rosuvastatin on repeat heart failure hospitalizations: the CORONA Trial (Controlled Rosuvastatin Multinational Trial in Heart Failure). *JACC Heart Fail.* 2014;2(3):289–97.
 - 65 Preiss D, Campbell RT, Murray HM, Ford I, Packard CJ, Sattar N, et al. The effect of statin therapy on heart failure events: a collaborative meta-analysis of unpublished data from major randomized trials. *Eur Heart J.* 2015;36(24):1536–46.
 - 66 Rauchhaus M, Coats AJ, Anker SD. The endotoxin-lipoprotein hypothesis. *Lancet.* 2000;356(9233):930–3.
 - 67 Tousoulis D, Charakida M, Stefanadi E, Siasos G, Latsios G, Stefanadis C. Statins in heart failure. Beyond the lipid lowering effect. *Int J Cardiol.* 2007;115(2):144–50.
 - 68 Xu M, Yuan G, Wei F. Effect of atorvastatin in patients with chronic heart failure - insights from randomized clinical trials. *Arch Med Sci.* 2010;6(6):866–73.
 - 69 Hare JM, Johnson RJ. Uric acid predicts clinical outcomes in heart failure: insights regarding the role of xanthine oxidase and uric acid in disease pathophysiology. *Circulation.* 2003;107(15):1951–3.
 - 70 Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. *Am J Med.* 1987;82(3):421–6.
 - 71 Givertz MM, Anstrom KJ, Redfield MM, Deswal A, Haddad H, Butler J, et al. Effects of Xanthine Oxidase Inhibition in Hyperuricemic Heart Failure Patients: The Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) Study. *Circulation.* 2015;131(20):1763–71.
 - 72 Hare JM, Mangal B, Brown J, Fisher C, Jr., Freudenberger R, Colucci WS, et al. Impact of oxypurinol in patients with symptomatic heart failure. Results of the OPT-CHF study. *J Am Coll Cardiol.* 2008;51(24):2301–9.
 - 73 Keenan T, Zhao W, Rasheed A, Ho WK, Malik R, Felix JF, et al. Causal Assessment of Serum Urate Levels in Cardiometabolic Diseases Through a Mendelian Randomization Study. *J Am Coll Cardiol.* 2016;67(4):407–16.
 - 74 Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. *Proc Natl Acad Sci U S A.* 1981;78(11):6858–62.
 - 75 Thanassoulis G, Brophy JM, Richard H, Pilote L. Gout, allopurinol use, and heart failure outcomes. *Arch Intern Med.* 2010;170(15):1358–64.
 - 76 Jankowska EA, von Haehling S, Anker SD, Macdougall IC, Ponikowski P. Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. *Eur Heart J.* 2013;34(11):816–29.
 - 77 Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med.* 2009;361(25):2436–48.
 - 78 Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J.* 2015;36(11):657–68.

- 79 Jankowska EA, Tkaczyszyn M, Suchocki T, Drozd M, von Haehling S, Doehner W, et al. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. *Eur J Heart Fail*. 2016. Epub Jan 28.
- 80 Rocca H-PB-L, Crijns HJGM. Iron i.v. in heart failure: ready for implementation? *Eur Heart J*. 2015;36(11):645–7.
- 81 Pieske B, Butler J, Filippatos G, Lam C, Maggioni AP, Ponikowski P, et al. Rationale and design of the SOLuble guanylate Cyclase stimulator in heart failure Studies (SOCRATES). *Eur J Heart Fail*. 2014;16(9):1026–38.
- 82 Krum H, Massie B, Abraham WT, Dickstein K, Kober L, McMurray JJV, et al. Direct renin inhibition in addition to or as an alternative to angiotensin converting enzyme inhibition in patients with chronic systolic heart failure: rationale and design of the Aliskiren Trial to Minimize OutcomeS in Patients with HEart failure (ATMOSPHERE) study. *Eur J Heart Fail*. 2011;13(1):107–14.
- 83 Zannad F, Greenberg B, Cleland JG, Gheorghiade M, van Veldhuisen DJ, Mehra MR, et al. Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial. *Eur J Heart Fail*. 2015;17(7):735–42.
- 84 McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993–1004.
- 85 Feldman AM, Haller JA, DeKosky ST. Valsartan/Sacubitril for Heart Failure: Reconciling Disparities Between Preclinical and Clinical Investigations. *JAMA*. 2016;315(1):25–6.
- 86 Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;351(6):543–51.
- 87 Pitt B, Kober L, Ponikowski P, Gheorghiade M, Filippatos G, Krum H, et al. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. *Eur Heart J*. 2013;34(31):2453–63.
- 88 Pitt B, Anker SD, Böhm M, Gheorghiade M, Køber L, Krum H, et al. Rationale and design of MinerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF): a randomized study of finerenone vs. eplerenone in patients who have worsening chronic heart failure with diabetes and/or chronic kidney disease. *Eur J Heart Fail*. 2015;17(2):224–32.
- 89 Packham DK, Rasmussen HS, Lavin PT, El-Shahawy MA, Roger SD, Block G, et al. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med*. 2015;372(3):222–31.
- 90 Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med*. 2015;372(3):211–21.
- 91 Jullig M, Hickey AJ, Chai CC, Skea GL, Middleditch MJ, Costa S, et al. Is the failing heart out of fuel or a worn engine running rich? A study of mitochondria in old spontaneously hypertensive rats. *Proteomics*. 2008;8(12):2556–72.
- 92 Doehner W, Frenneaux M, Anker SD. Metabolic impairment in heart failure: the myocardial and systemic perspective. *J Am Coll Cardiol*. 2014;64(13):1388–400.
- 93 Sparagna GC, Chicco AJ, Murphy RC, Bristow MR, Johnson CA, Rees ML, et al. Loss of cardiac tetralinoleoyl cardiolipin in human and experimental heart failure. *J Lipid Res*. 2007;48(7):1559–70.
- 94 Szeto HH. First-in-class cardiolipin-protective compound as a therapeutic agent to restore mitochondrial bioenergetics. *Br J Pharmacol*. 2014;171(8):2029–50.
- 95 Madmani ME, Yusuf Solaiman A, Tamr Agha K, Madmani Y, Shahrour Y, Essali A, et al. Coenzyme Q10 for heart failure. *Cochrane Database Syst Rev*. 2014;6:CD008684.
- 96 Mortensen SA, Rosenfeldt F, Kumar A, Dolliner P, Filipiak KJ, Pella D, et al. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. *JACC Heart Fail*. 2014;2(6):641–9.

Figures (large format)

**Figure 1**

Overview on current therapies for heart failure with reduced ejection fraction (HFrEF). The pyramid depicts the step-wise approach of adding evidence-based treatments as recommended by the 2012 ESC guidelines [9]. The white boxes reflect additional factors that are important for the treatment of HFrEF independent of the standard treatments. Not all therapies are subjects of this review and for detailed recommendations review of the guidelines is recommended [5].

*An ARB is recommended when an ACEI is not tolerated

** The position of ARNIs in the treatment cascade will be defined in the next ESC heart failure guidelines and was thus not more clearly defined in this figure.

ACEI = angiotensin converting-enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; CRT = cardiac resynchronisation therapy; ICD = implantable cardioverter defibrillator; H-ISDN = hydralazine-isosorbide dinitrate; HTx = heart transplantation; MCS = mechanical circulatory support; MRA= mineralocorticoid antagonist; omega3 = omega-3 polyunsaturated fatty acids; Q10 = coenzyme Q10.